REMARKS

Reconsideration of this application, as amended, is respectfully requested.

A. Status of the claims

Claims 433-437, 439-446, and 447-494 were pending in this application. Claims 439, 440, 444, and 447-494 were cancelled without prejudice or disclaimer. The Applicants reserve the right to pursue the cancelled claims in a separate continuation application. Claim 445 was amended to change the dependency from a now cancelled claim. Claim 433 was amended to further clarify the invention. Support for the amendment of claim 433 can be found in the specification in cancelled claims 439, 440 and 444 as well as page 33, line 1 to page 34, line 4. Accordingly, no new matter has been added to this application as a result of this amendment. Claims 433-437 and 439-446 are now pending in this application.

The Applicants respectfully request that the Examiner enter this amendment into the case and submit that the amendment of the claims places the application into condition for an allowance or in better form for consideration on appeal. Furthermore, the amendment does not raise any new issue that would impose any undue search burden on the Examiner.

B. Rejection under 35 U.S.C. section 102(e) or 103(a) in view of Kossovsky, Kausch, Yguerabide, and Chavany

As a threshold matter, the Federal Circuit has stated that for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. Corning Glass Works v. Sumitomo Electric, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 U.S.P.Q 193, 1098 (Fed. Cir. 1983).

Likewise, the Federal Circuit reiterated the manner in which obviousness rejections are to be reviewed. Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, "a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out,

those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1485 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988).

Contrary to the Examiner's position, the Applicants submit that neither Kossovsky, Kausch, Yguerabide, Chavany, nor Coffer teach or suggest what the Applicants have done.

1. **Kossovsky**

Claims 433-437 and 439-446 stand rejected under 35 U.S.C. section 102(e) as being anticipated by, or in the alternative, under 35 USC section 103(a) as being obvious over Kossovsky et al. (U.S. Patent no. 5,460,831)("Kossovsky"). The Examiner alleged that Kossovsky teaches or suggests the presently claimed composition, relying on the Abstract, cols. 3 and 4, and Examples 1-13 for support. The Applicants respectfully traverse this rejection.

The present invention, as claimed, is directed to nanoparticles having at least two types of oligonucleotides attached thereto, wherein "the oligonucleotides being present on a surface of the nanoparticles at a surface density of at least 10 picomoles/cm^2" and wherein at least one type of oligonucleotides comprises recognition oligonucleotides, the recognition oligonucleotides comprising a spacer portion and a recognition portion, the recognition portion having a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide; and a second type of oligonucleotides comprises diluent oligonucleotides, wherein the spacer portion of the recognition oligonucleotides and diluent oligonucleotides have functional groups that are attached to the nanoparticles. The Applicants have discovered, surprisingly, that the claimed nanoparticles-oligonucleotide conjugates having increased stability under storage and hybridization conditions can be made and that increased nanoparticle conjugate stability is observed when the surface density of oligonucleotides on the nanoparticles is at least 10 picomoles/cm^2. See the specification at page 78, lines 14-26. Moreover, the Applicants have discovered, surprisingly, that the inclusion of diluent oligonucleotides in addition to recognition oligonucleotides in nanoparticle-oligonucleotide conjugates provides a means of tailoring the nanoparticle conjugates to give a desired level of hybridization. See the specification at page 80, lines 8-27.

The Applicants respectfully submit that the Examiner's reliance on Kossovsky is misplaced as none of the cited portions of Kossovsky support the Examiner's allegations. Kossovsky merely relates to targeted transfection nanoparticles. See Abstract. The transfection nanoparticles consist of nanoparticle cores (see cols 3 and 4) that are coated with carbohydrates or other materials such as cellobiose, P5P, or citrate films (Examples 1-8, 11). The coated cores are then ready to absorb various transfection agents (Examples 12 -14). For instance, Kossovsky relates to absorbing purified DNA or RNA fragments of the human deaminase gene to coated cores (Example 12), absorbing sonicated viral particles and phospholipids membranes to coated cores (Example 13), and absorbing a human deaminase gene expression cassette and LDL membrane proteins to the coated cores. Nowhere in Kossovsky's disclosure does he teach or suggest nanoparticles having "at least two types of oligonucleotides attached thereto, the oligonucleotides being present on a surface of the nanoparticles at a surface density of at least 10 picomoles/cm^2. In addition, Kossovsky is completely silent with respect to the use of diluent and recognition oligonucleotides. Moreover, Kossovsky is completely silent with respect to oligonucleotides having "functional groups that are attached to the nanoparticles". See claim 433.

Accordingly, withdrawal of the section 102(e) and/or 103(a) rejection against the claims based on Kossovsky is in order and is respectfully requested. In addition, the Applicants further submit that Kossovsky does not teach or suggest the claimed detection method of new claims 447-494 and thus this reference cannot be applied to support a rejection of the new claims.

2. <u>Kausch</u>

Claims 433-437 and 439-446 stand rejected under 35 U.S.C. section 102(e) as being anticipated by, or in the alternative, under 35 USC section 103(a) as being obvious over Kausch al. (U.S. Patent no. 5,665,582)("Kausch"). Specifically, the Examiner alleged that Kausch teaches nanoparticle-oligonucleotide conjugates having the presently recited surface density range, relying on the Abstract, Col. 4-10, 17-19, 24 and Examples 1, 2 and 4-8 for support. The Applicants respectfully traverse this rejection.

Contrary to the Examiner's position, Kausch does not support the Examiner's allegations. Kausch merely relates to a separation method for isolating biological materials. See Kausch's Abstract. Kausch first anchors the biological material onto a solid support such as a glass slide

or coverslip coated with a reversible linker. See Kausch at col. 4, line 38 ("Summary of the invention") to col. 5, line 35. The anchored biological material is then labeled with a binding composition which may include magnetic or paramagnetic particles. See Kausch at ccol. 5, lines 46 to col. 6, lines 24. The labeled biological material is then released from the support and the released material is sorted by a magnetic force. See Kausch's abstract and cols. 4-10, particularly col. 6, lines 24-44 and col. 9, lines 44 to col. 10, line 16. Example 1 described isolation and anchoring of mouse DNA onto glass cover slips and use of magnetic particles to sort out the DNA. See col. 28, line 51 to col. 29, line 3. Example 2 also described anchoring chromosomes onto an alginate cushion, followed by detachment of the chromosomes and sorting using magnetic particles. Examples 4 (col. 39 – use of magnetic particles for sorting), 5 (col. 44 – preparation of magnetic particles), 6 (cols. 44 and 45 – conventional flow cytometry), 7 (cols. 45-50 – anchoring biological material to support, detachment of biological material from support, and sorting by magnetic particles) and 8 (cols. 50-52 – anchoring biological material to support, detachment of biological material from support, and sorting by magnetic particles).

Nowhere in Kausch's disclosure does he teach or suggest nanoparticles having "at least two types of oligonucleotides attached thereto, the oligonucleotides being present on a surface of the nanoparticles at a surface density of at least 10 picomoles/cm^2. In addition, Kausch does not teach or suggest nanoparticles having recognition oligonucleotides and diluent oligonucleotides attached thereto. Furthermore, Kausch does not teach or suggest olignonucleotides having functional groups for attaching to nanoparticles.. See claim 433. Accordingly, withdrawal of the section 102(e) and/or 103(a) rejection against the claims based on Kausch is in order and is respectfully requested

3. Yguerabide

Claims 433-437 and 439-446 stand rejected under 35 U.S.C. section 102(e) as being anticipated by, or in the alternative, under 35 USC section 103(a) as being obvious over Yguerabide (U.S. Patent No. 6,214,560)("Yguerabide"). The Applicants respectfully traverse this rejection.

Specifically, the Examiner alleged that Yguerabide taught detection and measurement of one or more analytes in a sample using particles of specific composition and size using light

scattering. The discussion is found starting in col. 82, line 35, of Yguerabide. Col. 83 provides further discussion regarding particle size and particle binding to a surface. Cols. 77-80 relate to particles and their preparation. Col. 110 (Example 32) relates to a nucleic acid labeled particle but does not provide or suggest any particle surface density. Indeed, no particle surface density can be calculated from Yguerabide's disclosure since he does not provide any DNA concentration. There is no discussion or suggestion anywhere in Yguerabide of a nanoparticle having any recognition and/or diluent oligonucleotides attached thereto and/or a particle surface density. The claims recite limitations that are neither taught, made obvious, or suggested by the cited reference. Thus, the Applicant respectfully submits that Yguerabide cannot be applied to support section 102(e) and/or section 103(a) rejections of the claims. Withdrawal of this rejection is in order and is respectfully requested.

4. Chavany

Claims 433-437, and 439-446 stand rejected under 35 U.S.C. section 102(e) as being anticipated by, or in the alternative, under 35 USC section 103(a) as being obvious over Chavany et al. (Pharmaceutical Research, Vol. 11: pp. 1370-1378)("Chavany"). Specifically, the Examiner alleged that Chavany teaches nanoparticle-oligonucleotide conjugates having the recited surface density, relying on pages 1370-1372, 1375 and 1377 for support. The Applicants respectfully traverse this rejection.

Contrary to the Examiner's position, none of the cited passages in Chavany support the Examiner's position. Chavany merely relates to the preparation of biodegradable transfection nanoparticles conjugates. Nucleic acid molecules that are associated with nanoparticles have increased resistance to nuclease degradation and increased cellular uptake and thus can be released to a body site for transfection purposes. The transfection nanoparticle conjugates are inherently unstable since the nanoparticles themselves are made of biodegradable polymers. See page 1370, 3rd paragraph. The transfection nanoparticles are formed by the absorption of oligonucleotides onto the nanoparticles. See Abstract and page 1371 under "Absorption of oligonucleotides to PIHCA nanoparticles". A disclosure of biodegradable nanoparticle conjugates with eenhanced nucleic acid stability to nuclease degradation is not a disclosure of the presently claimed nanoparticles. Nowhere in Chavany's disclosure does she teach or suggest

nanoparticles having "at least two types of oligonucleotides attached thereto, the oligonucleotides being present on a surface of the nanoparticles at a surface density of at least 10 picomoles/cm^2, wherein at least one type of oligonucleotides comprises recognition oligonucleotides. In addition, Chavany is completely silent with respect to any recognition and diluent oligonucleotides and the concept of oligonucleotides having functional groups for attaching to nanoparticles. See claim 433. Furthermore, Chavany does not provide any information, e.g., particle size, that would allow one to calculate any surface density of oligonucleotides on the nanoparticle surface. Accordingly, withdrawal of the section 102(e) and/or 103(a) rejection against the claims based on Chavany is in order and is respectfully requested.

E. Rejection under 35 U.S.C. section 102(b) in view of Coffer

Claims 433-436, 439-442, and 444-446 stand rejected under 35 U.S.C. section 102(e) as being anticipated by, or in the alternative, under 35 USC section 103(a) as being obvious over Coffer et al. (Nanotechnology, Vol. 3, lines 69-76 (1992))("Coffer"). The Examiner alleged that Coffer teaches a nanoparticle-oligonucleotide conjugate having the presently recited surface density, relying on pages 69-72 and 75 for support. The Applicants respectfully traverse this rejection.

Contrary to the Examiner's position, Coffer does not support the Examiner's allegations and is remote to the present invention. Coffer merely relates to CdS nanocrystallites stabilized by DNA and describes a two-step procedure of first mixing cadium ions with DNA to form a solution and adding sulfide to the solution to make a CdS cluster. See page 70-71. The DNA merely serves as a template for the formation and stabilization of CdS clusters. See page 71. While Coffer does mention the DNA concentration used in the solution for generating the CdS clusters, Coffer is completely silent with respect to the specific surface density of DNA at the surface of any nanoparticles. Indeed, nowhere in Coffer's disclosure does he teach or suggest nanoparticles having "at least two types of oligonucleotides attached thereto, the oligonucleotides being present on a surface of the nanoparticles at a surface density of at least 10 picomoles/cm^2, wherein at least one type of oligonucleotides comprises recognition oligonucleotides. In addition, Coffer is completely silent with respect to any recognition and diluent oligonucleotides and the concept of oligonucleotides having functional groups for attaching to nanoparticles. See

claim 433. Accordingly, withdrawal of the section 102(e) and/or 103(a) rejection against the claims based on Coffer is in order and is respectfully requested.

F. Conclusion

In conclusion, the Applicants respectfully submit that the claims in this application are in allowable condition and request a Notice to this effect.

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. The Examiner is invited to contact the undersigned representative if the Examiner believes that this would be helpful in expediting the prosecution of this application.

Respectfully submitted,

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